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THE BLOOD IN LEUKEMIA.*

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Leukemia is a malignant (idiopathic) hyperplasia affecting the leukocytic forming tissues, which results in an enormous increase in the production of the white blood corpuscles. This hyperplasia may affect only one type of cell, and there may even be a diminution of the other varieties of leukocytes, or there may be an increase of all varieties, with one type considerably more than the others.

Hughes Bennet in 1845 first described a case of suppuration of the blood or leukocythemia. A short time after 1845 Virchow described a case and gave it the name "leukemia." It was not however until some time later that Ehrlich, by his new method of staining, showed that in the two types, the cells were different.

The leukemias were formerly divided, according to their clinical aspects, into the lymphatic, splenic, spleno-medullary, and medullary or myelogenous forms. This has given way to the hematological one of Ehrlich of lymphatic and myeloid, based upon the kind of cell proliferation.

It has been shown by Nieman that in lymphatic leukemia the proliferation is not limited to the lymph glands alone, but may affect the lymphoid tissue of the spleen, the nodes and crypts of the intestines, and the bone marrow.

The enlargement of the spleen may be great, without any specific change in the character of the leukemiac process, or of the appearance of the blood. In spite of the splenic tumor the case is one of lymphatic leukemia. There has not been a single case of a pure splenic leukemia reported.

Acute lymphatic leukemia was first described by Friedich in 1857. (In a new case of leukemia.) These cases run an acute course with high fever, pronounced hemorrhagic diathesis, and terminate fatally in a short time. We have noted three such cases:

1st; A young man, 26 years of age, whose first symptom was a severe ulcerated throat, which became gangrenous. It showed a streptococcus infection and was treated for such. On further examination, on account of nasal hemorrhage, it was found he had an enlarged spleen. The blood showed 60,000 cells of the lymphocytic type. Death occurred in two days. Necropsy showed no special enlargement of the lymph glands. The spleen was quite large, but the bone marrow was typically that of lymphatic leukemia.

2nd; A woman of 36 with the same symptoms, with a gangrenous lymphatic pharyngeal ring, without a particularly marked general lymphatic enlargement. The bone marrow showed the typical leukemic changes.

3rd; A child of 5 with what was diagnosed as malaria, but upon examination of the blood a lymphatic leukemia was found. This child grew rapidly worse and died in two weeks.

The cells in these cases were of the lymphoblastic type, with a large nucleus and small rim of deep staining cytoplasm. The parent cell is the lymphoblastic macro-lymphocyte, or large lymphocyte. Their appearance in the blood except in children denotes an acute or chronic leukemia. They present the same characteristics as the small variety except in their great size, and that they contain two nucleoli. Amitosis is present. In some mild chronic cases the cells are not nearly so large, in fact are about the size of the ordinary small lymphocyte. In one case a man with a large spleen who was very anemic, was found to have a marked anemia of the primary type. His leukocytes were 4,000 with a differential count of 98% of small lymphocytes. It was shown that it was a lymphatic leukemia in which there was an anemia of the primary type. Upon rest in bed and treatment, the leukocytes gradually increased in number until in one month there were 160,000. all of the small variety; shortly after larger ones appeared, then the lymphoblasts. He died shortly after. Necropsy showed a moderate enlargement of the spleen with a few mesenteric lymph glands enlarged, but others not enlarged. The bone marrow was typically lymphoid. The difference between the above lymphoblasts and lymphoid myelocytes or leukoblasts (Pappenheim) is that the latter is a feebly basophile lymphoid cell with the nucleus of a myelocyte but the cytoplasm is devoid of neutrophil or eosinophile granules. They do contain however an azurophile substance such as is seen in both normal and pathological varieties of lymphoid cells.

They are now granular myelocytes with basic cytoplasm. This leukoblast with large indented nucleus is a sort of pathological monocyte and can

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seldom be distinguished from the macro-lymphocyte, or the monocyte of normal blood. The lymphoidocyte is often markedly basophilic and beset with a (myeloid) azur substance; its nucleus is leptochromatic and frequently contains several sharply defined nucleoli. It has a basic protoplasm. The nucleus stains pale in comparison to the surrounding narrow zone of more or less strongly basophilic cytoplasm.

Between these cells and the fully developed myelocyte there are various stages of genetic transition. The nucleus becomes more round, more basophilic and contains a fair number of neucleoli. These are the cells which are present in acute myeloblastic leukemia.

Just as the macrolymphocyte is the precursor of the small lymphocyte, so the lymphoidocyte gives rise to a daughter strain in the small pathological lymphocytes formed in the bone marrow, or myelo lymphocytes, which are remarkably similar to normal lymphatic lymphocytes. These macro lymphoidocytes stain like the lymphoidocytes.

In the acute leukemias, these forms are seen, especially in infiltrations. It is difficult to differentiate between the large celled lymphatic leukemia and a myeloblastic leukemia. The so-called mixed type of leukemia, or in those types in which there is a so-called change to the myelogenous type, that the forerunning cells were really lymphoidocytes and myeloblasts, and not true lymphoblasts. This is observed in chloroma, where there are microscopic infiltrations and even small tumor masses. This condition is now conceded to belong to the myelogenous type, rather than the lymphatic.

In the myeloid type there is an absolute increase of several varieties of cells, mostly of the granular type. There is also an absolute, though not a relative increase in the lymphocytes, polymorphs and eosinophiles. These granular cells descend from the leukoblast or myeloblast through the promyelocytes, the myelocyte, the metamyelocyte, to the polymorphs. Here it is most difficult to form a line of division between the metamyelocyte with its slightly irregular or deeply indented nucleus and clearly neutrophilic protoplasm, and the true polymorphs. It has been observed by me that a large number of these cells, when stained with Wright's stain, show at their border a deep blue rim of rod-like granules. Owing to the lack of a definite line of division, one is apt to err on the side of the myelocyte in making a differential count. It occurred to me that one method of settling this would be by determining their functional power. By using a cream of the leukocytes from a case of myelogenous leukemia, I tested their phagocytotic power, and found that the so-called metamyelocytes took up the bacteria just as well as did the polymorphs, while the neutrophilic, basophilic, eosinophilic myelocytes did not engulf them at all. These metamyelocytes are also noted in cases of irritative or toxic leukocytosis. So I would class them as young polymorphs and count them as such.

In the myeloid form the bone marrow shows a great hyperplasia of these elements, and so the lymphatic forms show lymphocytes. Some believe that they are always distinctly separate diseases. In some cases there need be little change in the spleen or lymph glands, being confined to the bone marrow. (This was nicely illustrated by one case of lymphatic in which the symptoms were those of a tabes dorsalis, and only when the blood was taken for a Wassermann was the true condition found. In this case there was no enlargement of the spleen or lymphatics.) However, hyperplasia may take place in any of the blood-forming organs or possibly two or more at the one time, then extend to the whole system, though some,—Nieman, Pappenheim and Grawitz,—claim that it always arises from the bone marrow. Its method of spreading to the general system is not known, whether by metastasis, as in tumor growth (Banti, Warthin), or to stimuli which causes the primary foci (Ehrlich, Lazarus, Pincus). Their claim is that there are two kinds of marrow, the lymphatic corresponding to the lymphatic organs, and the medullary; that when the entire bone marrow is stimulated, myeloid leukemia results, and when the lymphatic tissue, the lymphocytic type. They admit however a primary stimulus to the spleen and lymph glands, causing an increase in size, as in pseudo-leukemia; and that the lymphatic tissue of the bone marrow is secondarily involved; that owing to the unyielding character of the bone, the lymphocytes are forced, as it were, into the circulation.

It would seem that myeloid transformation could be regarded as a return of the blood-forming organs to their embryonic activity, as in some cases of lymphatic leukemia, a myeloid transformation is found in the lymph glands. There is however a general infiltration of all the organs and their sinuses with these cells.

Ehrlich defines lymphatic leukemia as belonging to tumor growth or functional overactivity, and myelogenous to a form of exaggerated leucocytosis, where the different varieties of granular cells react to a stimulus, or chematactic reaction. It is thought by many that both types are due to a common pathogenesis of unknown origin. There have been claims that it was due to a spirochete. Levit claimed a motile hemameta. These have not been confirmed.

Hirschfield and Jacoby claimed to have transmitted it in the leukemia of chickens, even using a filterable virus, which has not been confirmed. Banti argues for a sarcomatosis, and it is surely difficult to tell the exact difference between the hyperplasia in leukemia and the neoplastic overgrowth in sarcoma, their histology being so close, and as there are all grades from benign lymphoma pseudoleukemia, to lymphatic leukemia, and lymphosarcoma.

Warthin regards these different types of lymphocytoma as genetically related, being the same disease with different degrees of severity. Some are leukemic on account of the excess of leukocytes in the circulation, some aleukemic, both showing the same infiltration, and that aleukemic cases become leukemic. He divides them into

Aleukemic (1) where there is no absolute or relative increase in cells; (2) where there is a normal count and relative increase; (3) a pure typical lymphatic leukemia; and lymphosarcoma with great excess of cells with a large percentage of lymphocytes. With this he includes chloroma, with its greenish tumors and leukemic blood, and the myelomata showing myelocytes in the blood.

Secondary leukocytosis and lymphocytosis are often seen and indicate irritation of the hemopoetic organs. That is a reactionary condition, due to an irritation of a chemotactic nature, or due to a primary irritation as a direct toxic metaplasia of the leukoblastic tissue. The former is an active and the latter a passive leucocytosis.

The leukemias due to hyperplasia and the leukocytosis resulting from a toxic metaplasia are of a passive nature, i. e. repulsion leukocytosis. Functional leukocytosis and lymphocytosis due to chemotaxis are of active or reactionary character. Generally however active functional leukocytosis is associated with some cause leading to metaplasia. Acute leukemias due to an infection ought perhaps rather be classed among the metaplastic leukocytosis rather than among the actual hyperplastic leukemias. At the same time transition forms might exist between the toxic metaplasia on one hand and metahyperplasia on the other; that is, a hyperplasia combined with a metaplasia.

In certain infectious diseases after the administration of certain drugs, and protein, we may have a decided leukocytosis with myelocytes, lymphoidocytes, and especiallly large numbers of *meta myelocytes,* as in diphtheria pneumonia. That is a reactionary metaplasia. After such drugs as philocarpine, tuberculin, whooping cough, we have the large unripe lymphocyte.

On the other hand, during the course of a leukemia, there may be a great reduction of cells with intercurrent severe infections, as sepsis and erysipelas. These generally terminate fatally, or the picture resumes itself after the trouble has subsided. A pernicious anemia may take place with a leukopena. Hence the old term "aleukemic leukemia of Von Leube." As the patient recovers from the anemia the leukocytes increase. In one case where the spleen was extirpated some seven years ago, shortly after the operation the blood showed 80,000 cells with 20% of myelocytes. In a few weeks the number of cells was reduced to 11,000, where they remained three years. The blood showed a perfect picture of a primary enemia, though the reds were 4,000,000. The Hb was 90%. There still remained 5% of myelocytes in the blood. The patient is still alive and apparently well, though an examination of the blood has not been made for some time. He has suffered a severe pneumonia with emphysema following and has fully recovered.

ROENTGEN RAY TREATMENT OF LEUKEMIA.*

By HOWARD E. RUGGLES, M.D., San Francisco.

Since the cases of Schultz in 1901, Pusey in 1902 and Senn in 1903, the reported cases of leukemia treated with Roentgen rays run well into the thousands.

The usual results are more or less rapid improvement in general condition, lowering of white count, and return of differential count to normal. Subsequent relapses are common and are usually difficult to control. Faithful persistence with the treatment and intelligent dosage diminish the possibilities of relapse. There are a good many cases in the records which have been symptomatically well for periods of over five years. Contraindications are: 1, acute type; 2, presence of increasing anemia, cachexia, or fever.

Pathology. The primary effect of radiation is degenerative. In 10 to 14 days lymphocytes, myelocytes, myeloblasts, and even polymorphonuclears show swelling of nucleus and fragmentation of chromatin. Protoplasm is at first unchanged; later it becomes clear or vacuolated, and then the cells disappear. After prolonged courses of radiation a secondary reactive effect appears. Myeloid cells completely disappear from the lymph nodes and spleen and the organ becomes a fibroid mass containing scattering lymphoid cells. Spleens frequently show anemic infarcts, thrombosis of vessels and obliterating endarteritis.

Technic. Success depends entirely on the way radiation is given. There is considerable discussion as to whether the long bones or the spleen should be exposed. Probably the best results are obtained by exposing both, although the following report of a case which we have been treating at St. Luke's for two years shows that treatment of the spleen alone will give the desired result. As to actual technic, we use a tube backing up a five and one-half inch spark, a target skin distance of 10 inches, 1 mm. of aluminum filter and an exposure of 20 milliampere minutes. With our apparatus that is one-half an erythema dose; it is applied every two weeks alternately on abdomen and on back.

Our case is a girl who came to the hospital February 9, 1913, complaining of weakness, shortness of breath and pains in arms and legs which had lasted two months.

Examination showed a somewhat undersized girl of 13, with a spleen two inches below and two inches to the right of the umbilicus, with a white count of from 250,000 to 600,000.

X-rays were started at once, but in weak doses which did very little good. Benzol was tried for a short time with no effect. In August, 1913, the present technic was begun. The count began to fall immediately, and to-day the girl is absolutely

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